

Claims 1, 20, 23, 32 and 35 are amended to specify that the binding agent is of low-viscosity grade having a viscosity of about 10-200 cP or a degree of substitution range from 0.65-0.90. Similarly, claims 17 and 31 are amended to specify that the preferred binding agent, carboxymethylcellulose, is of low-viscosity grade having a viscosity of about 10-200 cP or a degree of substitution range from 0.65-0.90. Support for this amendment appears in the specification at p. 45 , line 21 to p. 46, line 14.

The amendment introduces no new matter. Applicants request reconsideration of the pending claims in light of the above proposed amendments and the following remarks.

#### **Summary of the Invention**

Applicants disclose that the viscosity of the carboxymethylcellulose (CMC) used to formulate an osteogenic device is critical for bone formation. Contrary to the teachings in the art, applicants have discovered that high-viscosity CMC adversely affects bone formation when used in an osteogenic device comprising a matrix as defined herein. When a synthetic polymer matrix is used, high-viscosity CMC can be used to induce bone formation. However, when a material as defined in claim 1 (i.e., not a synthetic polymer or demineralized bone) is used as a matrix (e.g., collagen), the osteogenic device must be formulated with low-viscosity CMC (approximately 10-50 cP, or 50-200 cP) in order to induce bone and /or cartilage formation (specification at p. 46, lines 6-14). This is an unexpected result and would not have been known by one of ordinary skill in the art.

**Rejections Under 35 U.S.C. § 102(b)**

**I**

Claims 1, 7-9, 11-14 and 20-24 remain rejected as allegedly anticipated by Ammann (WO 94/15653). Specifically, the Examiner asserts that applicants' previous argument that Ammann does not specifically teach the combination of collagen and CMC was found not persuasive. Office Action, p. 2, lines 16-17. Applicants respectfully traverse in light of the proposed amendments.

As amended, base claims 1, 20 and 23 specify that the claimed device must include a low-viscosity binding agent having a viscosity of about 10-200 cP or a degree of substitution range from 0.65-0.90. Ammann does not suggest or teach this feature.

On the contrary, Ammann provides at best a general suggestion of combining a laundry list of carbohydrates and/or insoluble proteins with hundreds of possible combinations and no specific teaching of combining collagen and low-viscosity CMC.

Thus, claims 1, 7-9, 11-14 and 20-24 are not anticipated by Ammann and applicants respectfully request withdrawal of this rejection.

**II**

Claims 20 and 22 remain rejected as allegedly anticipated by Beck (*J. Bone and Min. Res.* 6:1257-65, 1991). Specifically, the Examiner asserts that there is no teaching in the specification that would exclude TGF- $\beta$  from being an osteogenic protein. Furthermore, the Examiner contends that TGF- $\beta$  is an osteogenic protein as

is manifestly obvious from the teachings of Beck. Office Action, p. 3, lines 3-7.

Applicants respectfully traverse.

Applicants point out that osteogenic proteins are defined in the specification on p. 2, lines 15-23:

Thus, true osteogenic proteins are capable of inducing the above-described cascade of morphogenic events resulting in endochondral bone formation...these osteogenic factors...can induce recruitment of accessible progenitor cells and stimulate their proliferation, thereby inducing differentiation into chondrocytes and osteoblasts, and further inducing differentiation of intermediate cartilage, vascularization, bone formation, remodeling, and finally, marrow differentiation” (**emphasis added**).

The formation of a cartilagenous intermediate is a crucial step in the cascade of events that lead to formation of endochondral bone.

In contrast, Beck states on p. 1262 that:

“a single application of TGF- $\beta$ 1 to a skull defect is sufficient to induce the cascade of events that result in bone formation. However, although bone formation continues until complete closure occurs, this occurs without evidence of cartilagenous intermediate. In contrast, BMPs admixed with demineralized bone powders and implanted at soft tissue sites or sites of bony defects induce bone with a cartilagenous intermediate” (**emphasis added**).

Thus, according to Beck, TGF- $\beta$  does not induce intermediate cartilage formation which is a required step in the cascade of morphogenic events resulting in endochondral bone formation as defined for osteogenic proteins in the specification.

Indeed, as shown in Sampath<sup>2</sup> (Exhibit 1), TGF- $\beta$  does not lead to

---

<sup>2</sup> Sampath, T. K. et al., “Isolation of osteogenin, an extracellular matrix-associated, bone-inductive protein, by heparin affinity chromatography,” PNAS, 84, pp. 7109-7113 (1987).

cartilage formation, a crucial step in endochondral bone formation (p. 7112).

For all of the above reasons, claims 20 and 22 are not anticipated by Beck and applicants respectfully request the withdrawal of the rejection.

**Rejection Under 35 U.S.C. § 102(e)**

Claims 1-5, 7-9, 11-13, and 31 remain rejected as allegedly anticipated by Tucker (U.S. Patent 5,674,292). Office Action, p. 3, lines 8-10. Applicants respectfully traverse in light of the proposed amendments.

Amended base claims 1 and 31 now require that the claimed device comprise a low-viscosity binding agent with a viscosity of about 10-200 cP or a degree of substitution range from 0.65-0.90. This feature is nowhere taught or suggested in Tucker.

Thus, Tucker does not anticipate claims 1-5, 7-9, 11-13 and 31.

**Rejections Under 35 U.S.C. § 103(a)**

**I**

Claims 1-5 and 31 remain rejected as allegedly obvious over Ammann and Kuberasampath (U.S. Patent 5,645,591). Specifically, the Examiner asserts that Ammann teaches the polymer may be CMC or collagen or a combination of these on p. 10, lines 28-34. Furthermore, the Examiner states that it would have been obvious to make an osteogenic device comprising TGF- $\beta$ , as taught by Ammann, and modify that teaching by making an osteogenic device comprising OP-1, as taught by Kuberasampath, with a reasonable expectation of success. Office Action, p. 4, lines 7-11. Applicants respectfully traverse in light of the proposed amendments.

As applicants have argued above, amended base claims 1 and 31 specify that the claimed device must include a low-viscosity binding agent having a viscosity of about 10-200 cP or a degree of substitution range from 0.65-0.90. Nowhere is this feature taught by Ammann.

Furthermore, Kuberasampath discloses using a synthetic collagen-GAG polymer as a matrix material. Kuberasampath does not teach or even suggest the use of any matrix material other than a synthetic polymer of collagen-GAG, much less the use of a matrix material that is not a synthetic polymer. Kuberasampath's device contains a collagen-GAG synthetic polymer made artificially by cross-linking collagen and GAG (p. 8).

Thus, Ammann and Kuberasampath, either alone or in combination, do not provide a person of ordinary skill in the art with any teachings to arrive at an osteogenic device with the properties recited in amended claims 1-5 and 31.

## II

Claims 1, 6, 15, 16, 32, 33, 35 and 36 remain rejected as allegedly obvious over Ammann and Ogawa (*J. Biol. Chem.* 267: 14233-7, 1992). Ammann is applied by the Examiner as discussed above. Furthermore, the Examiner asserts that there is no teaching in the specification that would exclude TGF- $\beta$  from being an osteogenic protein. Office Action, p. 4, lines, 16-17 and p. 5, lines 2-3. Applicants respectfully traverse in light of the proposed amendments.

As discussed above, amended base claims 1, 32 and 35 recite that the

binding agent is a low-viscosity binding agent having a viscosity of about 10-200 cP or a degree of substitution range from 0.65-0.90. Neither Ammann nor Ogawa, alone or in combination, teaches this feature. For these reasons, applicants request that the rejection be withdrawn.

### III

Claims 17-19 and 25 remain rejected as allegedly obvious over Ammann and Cook (*Clin. Ortho. Rel. Res.* 301: 302-312, 1994) in view of Ogawa. Ammann is applied by the Examiner as discussed above. According to the Examiner, Ammann teaches that the polymer may be CMC or collagen or a combination of these. Furthermore, the Examiner asserts that it would have been obvious to make an osteogenic device comprising TGF- $\beta$ 1, collagen and CMC, as taught by Ammann and modify that teaching by using 2.5 mg of OP-1/500 mg of collagen, as taught by Cook, and further modify that teaching by wetting the device with saline, as taught by Ogawa with a reasonable expectation of success. Office Action, p. 5, lines 10-18 and p. 6, lines 1-3. Applicant respectfully traverse.

As discussed earlier, Ammann does not teach or even suggest the feature of low-viscosity carboxymethylcellulose, as required in amended base claim 17. Cook and Ogawa, alone or in combination, do not remedy this deficiency. Thus, one of ordinary skill in the art would not have arrived at the claimed invention by combining the three cited references. Thus, the Examiner has failed to establish a *prima facie* case of obviousness and applicants request withdrawal of this rejection.

CONCLUSION

For all the above reasons, applicants request that the Examiner  
withdraw all outstanding rejections and grant allowance to the pending claims.

Respectfully submitted,



Z. Ying Li (Reg. No. 42,800)

Agent for Applicants

c/o FISH & NEAVE

1251 Avenue of the Americas

New York, New York 10020

Tel.: (212) 596-9000

## Appendix of Amendments

1. (Seven Times Amended) A device for inducing local bone or cartilage formation, comprising:
  - a purified osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects, said purified osteogenic protein being isolated from naturally-occurring sources or produced by recombinant DNA techniques;
  - a matrix; and
  - a binding agent selected from the group consisting of mannitol, dextran, cellulose, white petrolatum, and derivatives thereof;wherein the device does not comprise a synthetic polymer matrix or a demineralized bone matrix, and said binding agent has a viscosity of about 10-200 cP or a degree of substitution range from 0.65-0.90.
17. (Four Times Amended) A device for inducing local bone or cartilage formation, comprising at least approximately 1.25 mg of purified OP-1 and at least approximately 180 mg of carboxymethylcellulose per 1000mg of collagen matrix, wherein said purified OP-1 is isolated from naturally-occurring sources or produced by recombinant DNA techniques, and said carboxymethylcellulose has a viscosity of about 10-200 cP or a degree of substitution range from 0.65-0.90.
20. (Six Times Amended) A device for inducing local cartilage or bone formation comprising a purified osteogenic protein capable of inducing repair of



endochondral bone, or cartilage, chondral, or osteochondral defects and a carrier, wherein said carrier comprises one part binding agent and 10 or fewer parts (w/w) matrix, [and] said purified osteogenic protein is isolated from naturally-occurring sources or produced by recombinant DNA techniques, and said binding agent has a viscosity of about 10-200 cP or a degree of substitution range from 0.65-0.90.

23. (Six Times Amended) A device for inducing local bone or cartilage formation comprising a purified osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects and a carrier, wherein said carrier comprises 10 or fewer parts (w/w) binding agent and 1 part matrix, [and] said purified osteogenic protein being isolated from naturally-occurring sources or produced by recombinant DNA techniques, and said binding agent has a viscosity of about 10-200 cP or a degree of substitution range from 0.65-0.90.

31. (Three Times Amended) A device for inducing local bone or cartilage formation comprising:

- purified OP-1;
- collagen matrix; and
- carboxymethylcellulose;

wherein said purified OP-1 is isolated from naturally-occurring sources or produced by recombinant DNA techniques, and said carboxymethylcellulose has a viscosity of about 10-200 cP or a degree of substitution range from 0.65-0.90.

32. (Twice Amended) A kit for inducing local bone or cartilage

formation using the device of claim 1, the kit comprising:

(a) a receptacle adapted to house the osteogenic protein and the matrix material, and

(b) a receptacle adapted to house the binding agent,

wherein the osteogenic protein and matrix material are provided in the receptacle of part (a), and the binding agent is provided in the receptacle of part (b), and said binding agent has a viscosity of about 10-200 cP or a degree of substitution range from 0.65-0.90.

35. (Twice Amended) A kit for inducing local bone or cartilage formation using the device of claim 1, the kit comprising:

a first receptacle adapted to house the osteogenic protein, the matrix material, and the binding agent,

wherein the osteogenic protein, matrix material and binding agent are provided in said receptacle, and said binding agent has a viscosity of about 10-200 cP or a degree of substitution range from 0.65-0.90.